

We claim:

1. A method of making a controlled release composition comprising:
5 combining an organic phase comprising a bioactive agent and a polymer with an aqueous phase comprising an organic ion, wherein said organic ion is present in an aqueous phase to reduce degradation of said bioactive agent; and recovering said composition.
- 10 2. The method of claim 1, further comprising a cosolvent in said organic phase.
3. The method of claim 2, wherein said cosolvent is selected from the group consisting of dimethyl sulfoxide, dimethyl formamide, n-methylpyrrolidinone, PEG₂₀₀,
15 PEG₄₀₀, methyl alcohol, ethyl alcohol, isopropyl alcohol and benzyl alcohol.
4. The method of claim 1, further comprising an emulsifying agent in said aqueous phase.
- 20 5. The method of claim 4, wherein said emulsifying agent is selected from the group consisting of poly(vinyl alcohol), albumin, lecithin vitamin E -TPGS and polysorbates.
6. The method of claim 4, wherein said emulsifying agent is at a final
25 concentration ranging from about 0.1 to 10% (w/w).
7. The method of claim 1, wherein said organic phase comprises a solvent selected from the group consisting of methylene chloride, ethyl acetate, benzyl alcohol, acetone, acetic acid and propylene carbonate.
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8. The method of claim 1, wherein said organic ion is at a final concentration ranging from about 0.1 to 1000 mM.
9. The method of claim 1, wherein said controlled release composition is
35 selected from the group consisting of microparticles and nanoparticles.

10. The method of claim 9, wherein said microparticles and nanoparticles are biodegradable.

11. The method of claim 1, wherein said polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetyls, polycyanoacrylates, polyetheresters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers of polyethylene glycol and polyorthoester, biodegradable polyurethanes, blends and copolymers thereof.

12. The method of claim 1, wherein said bioactive agent is selected from the group consisting of proteins, nucleic acids, carbohydrates, peptides, LHRH agonists and synthetic analogs thereof, leuprolide, oxytocin, somatostatin and synthetic analogs thereof, small molecule pharmaceutical substances, immunogens, metabolic precursors capable of promoting growth and survival of cells and tissues, antineoplastic agents, hormones, antihistamines, cardiovascular agents, anti-ulcer agents, bronchodilators, vasodilators, central nervous system agents and narcotic antagonists.

13. The method of claim 12, wherein said protein or said peptide is selected from the group consisting of octreotide, oxytocin, insulin, leuprolide and synthetic variations thereof.

14. The method of claim 1 wherein the organic phase and aqueous phase are combined using an emulsion process.

15. The method of claim 14, wherein said emulsion process is selected from the group consisting of oil-in-water and water-oil-water.

16. The method of claim 1, wherein said organic ion is selected from the group consisting of carboxylate, sulfate, phosphate, pamoate, dodecylsulfate, trifluoromethyl-p-toluate, cholate, 2-naphthalene sulfonate, 2,3-naphthalene dicarboxylate, 1-hydroxy-2-naphthoate, 3-hydroxy-2-naphthoate, 2-naphthoate, and salicylsalicylate.

17. A controlled release composition made by the method of claim 1.

18. A process for the production of a microparticle comprising a bioactive agent in a polymer, which comprises the steps of:

- 5 a) combining a biodegradable polymer and an organic phase;
 b) combining a bioactive agent and said organic phase;
 c) combining an organic ion and an aqueous phase;
 d) contacting the organic and aqueous phases through the use of an emulsion process; and
10 e) recovering said microparticles.

19. The microparticle obtained according to claim 18.

20. The process of claim 18, further comprising a cosolvent in said organic
15 phase.

21. The process of claim 20, wherein said cosolvent is selected from the group consisting of dimethyl sulfoxide, dimethyl formamide, n-methylpyrrolidinone, PEG₂₀₀, PEG₄₀₀, methyl alcohol, ethyl alcohol, isopropyl alcohol and benzyl alcohol.
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22. The process of claim 18, further comprising an emulsifying agent in said aqueous phase.

23. The process of claim 22, wherein said emulsifying agent is selected from the group consisting of poly(vinyl alcohol), albumin, lecithin vitamin E -TPGS and polysorbates.
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24. The process of claim 22, wherein said emulsifying agent is at a final concentration ranging from about 0.1 to 10% (w/w).
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25. The process of claim 18, wherein said organic phase comprises a solvent selected from the group consisting of methylene chloride, ethyl acetate, benzyl alcohol, acetone, acetic acid and propylene carbonate.

35 26. The process of claim 18, wherein said organic ion is at a final concentration ranging from about 0.1 to 1000 mM.

27. The process of claim 18, wherein said controlled release composition is selected from the group consisting of microparticles and nanoparticles.

5 28. The process of claim 27, wherein said microparticles and nanoparticles are biodegradable.

29. The process of claim 18, wherein said polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic
10 acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetyls, polycyanoacrylates, polyetheresters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers of polyethylene glycol and polyorthoester, biodegradable polyurethanes, blends and copolymers thereof.

15 30. The process of claim 18, wherein said bioactive agent is selected from the group consisting of proteins, nucleic acids, carbohydrates, peptides, LHRH agonists and synthetic analogs thereof, leuprolide, oxytocin, somatostatin and synthetic analogs thereof, small molecule pharmaceutical substances, immunogens,
20 metabolic precursors capable of promoting growth and survival of cells and tissues, antineoplastic agents, hormones, antihistamines, cardiovascular agents, anti-ulcer agents, bronchodilators, vasodilators, central nervous system agents and narcotic antagonists.

25 31. The process of claim 30, wherein said protein or said peptide is selected from the group consisting of octreotide, oxytocin, insulin, leuprolide and synthetic variations thereof.

30 32. The process of claim 18, wherein said emulsion process is selected from the group consisting of oil-in-water and water-oil-water.

33. The process of claim 18, wherein said organic ion is selected from the group consisting of carboxylate, sulfate, phosphate, pamoate, dodecylsulfate, trifluoromethyl-p-toluate, cholate, 2-naphthalene sulfonate, 2,3-naphthalene
35 dicarboxylate, 1-hydroxy-2-naphthoate, 3-hydroxy-2-naphthoate, 2-naphthoate, and salicylsalicylate.

34. A controlled release composition made by the process of claim 18.

5 35. An improved process for the production of a microparticle comprising a bioactive agent in a polymer via an emulsion process, wherein said improvement consists of providing an organic ion in an aqueous phase to reduce degradation of the bioactive agent.

36. A method comprising:
10 a) combining a bioactive agent with an organic phase;
b) combining a polymer with said organic phase;
b) combining an organic ion with an aqueous phase; and
c) contacting the resulting organic and aqueous phases through the
use of an emulsion process to produce a controlled release composition including an
15 organic ion-bioactive agent complex.

37. The method of claim 36, further comprising a cosolvent in said organic phase.

20 38. The method of claim 37, wherein said cosolvent is selected from the group consisting of dimethyl sulfoxide, dimethyl formamide, n-methylpyrrolidinone, PEG₂₀₀, PEG₄₀₀, methyl alcohol, ethyl alcohol, isopropyl alcohol and benzyl alcohol.

39. The method of claim 36, further comprising an emulsifying agent in said
25 aqueous phase.

40. The method of claim 39, wherein said emulsifying agent is selected from the group consisting of poly(vinyl alcohol), albumin, lecithin vitamin E -TPGS and polysorbates.

30 41. The method of claim 39, wherein said emulsifying agent is at a final concentration ranging from about 0.1 to 10% (w/w).

42. The method of claim 36, wherein said organic phase comprises a solvent
35 selected from the group consisting of methylene chloride, ethyl acetate, benzyl alcohol, acetone, acetic acid and propylene carbonate.

43. The method of claim 36, wherein said organic ion is at a final concentration ranging from about 0.1 to 1000 mM.

5 44. The method of claim 36, wherein said controlled release composition is selected from the group consisting of microparticles and nanoparticles.

 45. The method of claim 44, wherein said microparticles and nanoparticles are biodegradable.

10 46. The method of claim 36, wherein said polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids),
15 polyorthoesters, polyacetyls, polycyanoacrylates, polyetheresters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers of polyethylene glycol and polyorthoester, biodegradable polyurethanes, blends and copolymers thereof.

20 47. The method of claim 36, wherein said bioactive agent is selected from the group consisting of proteins, nucleic acids, carbohydrates, peptides, LHRH agonists and synthetic analogs thereof, leuprolide, oxytocin, somatostatin and synthetic analogs thereof, small molecule pharmaceutical substances, immunogens, metabolic precursors capable of promoting growth and survival of cells and tissues, antineoplastic agents, hormones, antihistamines, cardiovascular agents, anti-ulcer
25 agents, bronchodilators, vasodilators, central nervous system agents and narcotic antagonists.

 48. The method of claim 47, wherein said protein or said peptide is selected from the group consisting of octreotide, oxytocin, insulin, leuprolide and synthetic
30 variations thereof.

 49. The method of claim 36, wherein said emulsion process is selected from the group consisting of oil-in-water and water-oil-water.

35 50. The method of claim 36, wherein said organic ion is selected from the group consisting of carboxylate, sulfate, phosphate, pamoate, dodecylsulfate,

trifluoromethyl-p-toluate, cholate, 2-naphthalene sulfonate, 2,3-naphthalene dicarboxylate, 1-hydroxy-2-naphthoate, 3-hydroxy-2-naphthoate, 2-naphthoate, and salicylsalicylate.

- 5 51. A controlled release composition made by the method of claim 36.